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(54) NOVEL IMIDAZOLE DERIVATIVE AND PROCESS FOR PRODUCING THE SAME

NEUE IMIDAZOL-DERIVATE UND VERFAHREN ZU DEREN HERSTELLUNG

NOUVEAU DERIVE DE L'IMIDAZOLE ET SA METHODE D'OBTENTION

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Description

Technical field

[0001] The present invention relates to therapeutic agents, which are novel imidazole derivatives, and is particularly concerned to imidazole derivatives being anticholinergic agents, especially selective antagonists against muscarinic acetylcholine receptor, process for preparing the same, and pharmaceutical compositions comprising them.

Background technologies

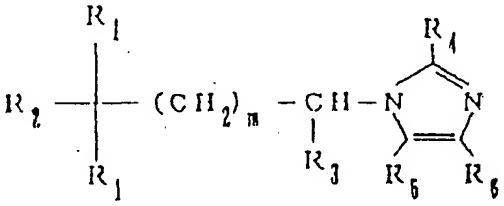
[0002] The anticholinergic agents exhibit anticonvulsant action and antisecretory action and have usefulness as the therapeutic agents for functional disorders of intestine, bladder, etc. At present, alkaloids such as atropine, aminoalkanol esters such as oxybutynin and propantheline bromide, their quaternary ammonium salts and the like have been known as the anticholinergic agents, and they are blocking agents for muscarinic acetylcholine receptor. However, because of their poor selectivity among organs in the antagonistic action, the side effects are caused and has posed problems. Therefore, the development of highly selective anticholinergic drug is desired in clinic.

[0003] Though, there is a report on 5-[1-(imidazole)methyl]-3,3-disubstituted-2(3H)-furanone derivatives as antagonists against muscarinic acetylcholine receptor, having imidazole group as a substituent, (Japanese Unexamined Patent Publication No. Hei 4-103581), these compounds are different from the inventive compounds in the structure, and yet they don't have adequate activity to satisfy.

[0004] The invention provides drugs having higher selectivity and more potent antagonistic activity on muscarinic acetylcholine receptor on smooth muscle than muscarinic acetylcholine receptor on heart.

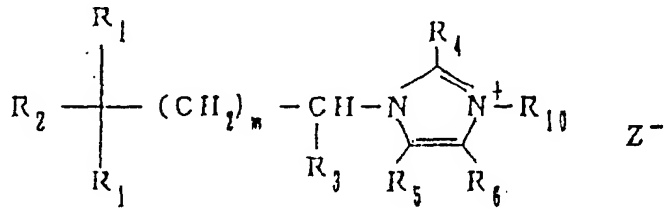
Disclosure of the invention

[0005] The inventors had focused on imidazole derivatives for the purpose aforementioned. As a result of diligent studies, so have found that imidazole derivatives represented by the general formula (1)



(1)

[wherein R_1 is a phenyl group which may have halogen substituent or a thienyl group, R_2 is a cyano group, carboxyl group; a $CONR_7R_8$ group (wherein R_7 and R_8 each independently represent hydrogen atom or straight or branched chain alkyl groups having from 1 to 6 carbon atoms, or R_7 and R_8 may form a ring by alkylene chain which may contain oxygen, sulfur or nitrogen hetero atoms) or a $COOR_9$ group (wherein R_9 is a straight or branched chain alkyl group having from 1 to 6 carbon atoms), R_3 is a hydrogen atom or a straight or branched chain alkyl group having from 1 to 6 carbon atoms, R_4, R_5 and R_6 each independently represent hydrogen atom, straight or branched chain alkyl groups having from 1 to 6 carbon atoms which may have substituents selected from the group consisting of halogen, straight or branched chain alkoxy group having from 1 to 6 carbon atoms, hydroxyl group and phenyl group, or cycloalkyl groups having 3 to 8 carbon atoms, and m is an integer from 1 to 6], or a general formula (2)



(2)

[wherein R_1, R_2, R_3, R_4, R_5, R_6 and m are defined as above, R_{10} is a straight or branched chain alkyl group having 1 to 6 carbon atoms or an aralkyl group with straight or branched chain alkylene having 1 to 6 carbom atoms bonded to phenyl group which may have a substituent selected from halogen, straight or branched chain alkyl group having 1 to 6 carbon atoms, straight or branched chain alkoxy groups having 1 to 6 carbon atoms bonded to oxygen atom, nitro group or phenyl group, and Z is a halogen atom],
have potent anticholinergic activity, especially selective and potent antagonistic activity on muscarine receptor of smooth muscles of alimentary canal, trachea, bladder, etc., and have brought the invention to completion.

[0006] By this reason, the inventive compounds are useful for the treatment of motility disorders of alimentary canal such as irritable bowel syndrome, diverticulum disease, functional diarrhea, esophageal achalasia and cardiospasm, treatment of biliary and urethral spasms, urinary incontinence, etc, treatment of chronic respiratory obstructive diseases, and the like.

[0007] The term "halogens" indicate fluorine, chlorine, bromine and iodine.

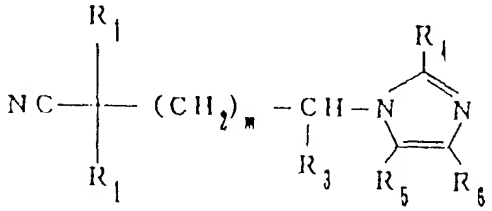
[0008] Examples of straight or branched chain alkyl groups with the number of carbons from 1 to 6 are methyl, ethyl and isopropyl.

[0009] Examples of straight chain or branched alkoxy groups with the number of carbons from 1 to 6 are methoxy group, ethoxy group and isopropoxy group.

[0010] Examples of cycloalkyl groups (alicyclic hydrocarbons) with the number of carbons from 3 to 8 are cyclopropyl and cyclohexyl.

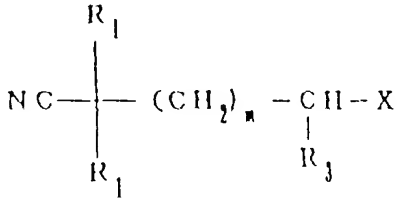
[0011] Examples of aralkyl groups with straight chain or branched alkylene group with the number of carbons from 1 to 6 bonded to phenyl group are benzyl and phenylethyl.

[0012] In the invention, compounds represented by a general formula (3)



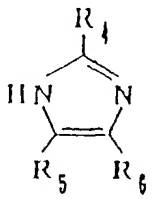
(3)

[wherein R_1, R_3, R_4, R_5, R_6 and m are as defined above], may be prepared by reacting compounds represented by a general formula (4)



(4)

[wherein, R_1, R_3 and m are as defined above, and X is a leaving group],
with compounds represented by a general formula (5)



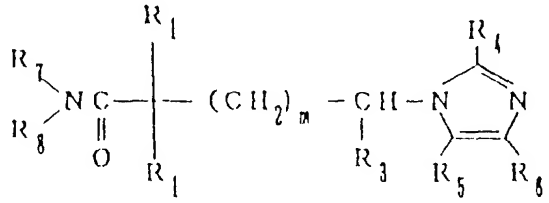
(5)

[wherein R_4, R_5 and R_6 are as defined above],
preferably in the presence of base.

[0013] Here, the term "leaving group" indicate halogen, aliphatic sulfonyloxy group such as methanesulfonyloxy group, arylsulfonyloxy group such as toluenesulfonyloxy group or the like.

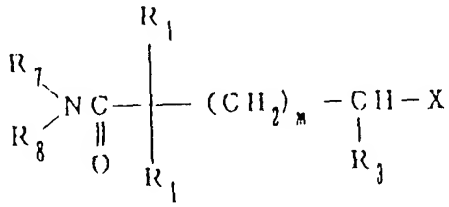
[0014] The reaction can be carried out at 0 to 200 °C, preferably at 60 to 150 °C in an organic solvent such as dimethylformamide, N-methylpyrrolidone, N,N'-dimethylimidazolidinone, dimethyl sulfoxide or xylene in the presence of inorganic base such as sodium hydroxide, potassium hydroxide, calcium hydroxide, sodium carbonate or potassium carbonate or organic base such as triethylamine or pyridine.

[0015] Moreover, in the invention, compounds represented by a general formula (6)



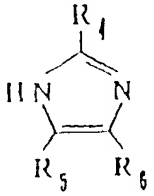
(6)

[wherein R_1, R_3, R_4, R_5, R_6, R_7, R_8 and m are as defined above] , may be prepared by reacting compounds represented by a general formula (7)



(7)

[wherein R_1, R_3, R_7, R_8 and m are as defined above, and X is a leaving group],
with compounds represented by the general formula (5)

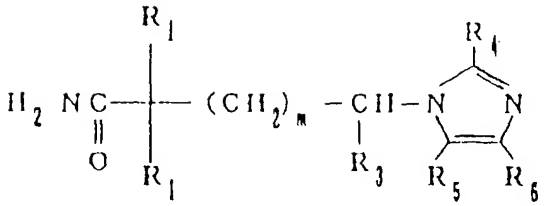


(5)

[wherein R_4, R_5 and R_6 are as defined above],
preferably in the presence of base.

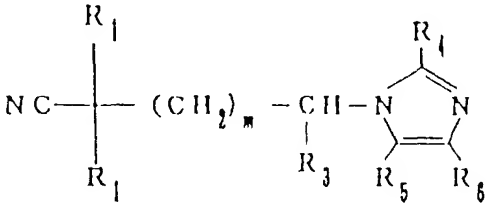
[0016] The reaction can be carried out at 0 to 200 °C, preferably at 60 to 150 °C in an organic solvent such as dimethylformamide, N-methylpyrrolidone, N,N'-dimethylimidazolidinone, dimethyl sulfoxide or xylene in the presence of inorganic base such as alkali metal hydroxide such as sodium hydroxide or potassium hydroxide, metal carbonate such as sodium carbonate or potassium carbonate or organic base such as triethylamine or pyridine.

[0017] Furthermore, in the invention, compounds represented by a general formula (8)



(8)

[wherein R_1, R_3, R_4, R_5, R_6 and m are as defined above],
may be prepared by hydrolysis of compounds represented by the general formula (3)

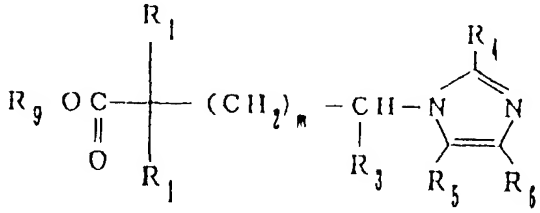


(3)

[wherein R_1, R_3, R_4, R_5, R_6 and m are as defined above].

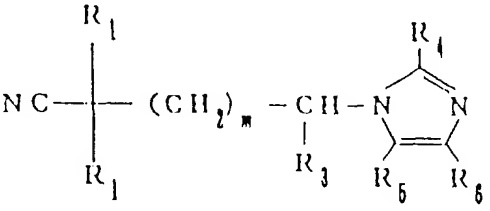
[0018] The reaction may be carried out at 0 to 150 °C, preferably at 100 to 150 °C in a aqueous acidic solution of sulfuric acid or polyphosphoric acid and the like or aqueous alkaline solution of sodium hydroxide or potassium hydroxide and the like.

[0019] Still more, in the invention, compounds represented by a general formula (9)



(9)

[wherein R_1, R_3, R_4, R_5, R_6, R_9 and m are as defined above], can be prepared by alcoholysis of compounds represented by the general formula (3)

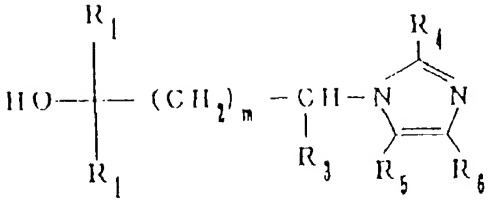


(3)

[wherein R_1, R_3, R_4, R_5, R_6 and m are as defined above].

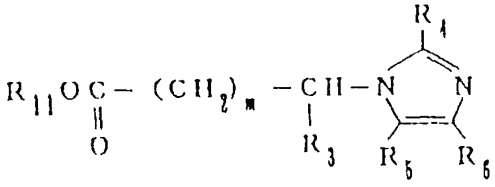
[0020] The reaction may be carried out at 0 to 150 °C, preferably at 100 to 150 °C in aqueous alcohol in the presence of inorganic acid such as sulfuric acid or organic acid such as p-toluenesulfonic acid.

[0021] Still more, compounds represented by a general formula (10)



(10)

[wherein R_1, R_3, R_4, R_5 R_6 and m are as defined above],
may be prepared by reacting compounds represented by a general formula (11)



(11)

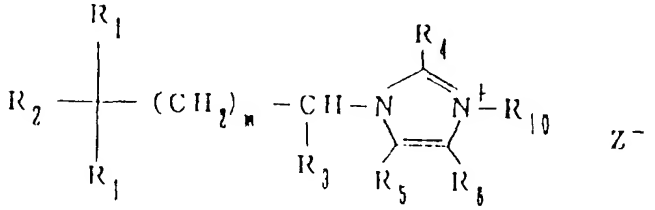
[wherein R_3, R_4, R_5, R_6 and m are as defined above, and R_{11} is a lower alkyl group],
with compounds represented by a general formula (12)

$$R_1 - Y \qquad (12)$$

[wherein R_1 is as defined above, and Y is lithium or magnesium halogenide],
under an inert gas.

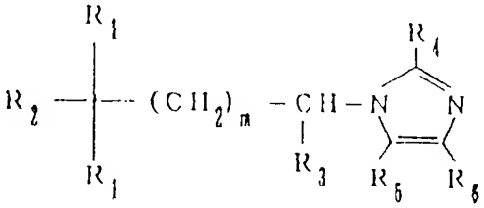
[0022] The reaction may be carried out at -78 to 30 °C in anhydrous tetrahydrofuran or ether.

[0023] Still more, compounds represented by the general formula (2)



(2)

[wherein R_1, R_2, R_3, R_4, R_5, R_6 R_{10} and m are as defined above, and Z is a halogen atom],
may be prepared by reacting compounds represented by the general formula (1)



(1)

[wherein R_1, R_2, R_3, R_4, R_5, R_6 and m are as defined above],
with compounds represented by a general formula (13)

$$R_{10} - Z \quad (13)$$

[wherein R_{10} and Z are as defined above],

[0024] The reaction can be carried out at 0 to 100 °C in an organic solvent such as acetone, ethanol, acetonitrile or dimethylformamide.

[0025] In the case of the inventive imidazole derivatives containing one or more asymmetric carbons, there will exist optical isomers. The invention includes these isomers and mixtures.

[0026] The novel compounds of the invention can be formed to acid addition salts with pharmaceutically acceptable inorganic acids, for example, hydrochloric acid, sulfuric acid, hydrobromic acid and phosphoric acid, or organic acids, for example, maleic acid, fumaric acid, acetic acid, oxalic acid, tartaric acid, benzenesulfonic acid, and the like, by conventional methods.

[0027] The inventive novel compounds can be administered orally in the form of tablets, capsules, granules, powders, inhalants, syrups or the like, or can be administrated by injections or suppositories or the like.

Best embodiment for putting the invention into practice

[0028] In following, the invention will be illustrated in detail based on the examples.

(Example 1)

4-(2-Methyl-1-imidazolyl)-2,2-diphenylbutyronitrile. hydrochloride

[0029] 4-Bromo-2,2-diphenylbutyronitrile (3.00 g, 10.0 mmol), 2-methylimidazole (2.46 g, 30.0 mmol), triethylamine (1.40 ml, 10.0 mmol) and dimethylformamide (50 ml) were mixed and stirred under heat for 30 hours at 150 °C in a sealed tube. The solution was poured into water, and was extracted with benzene. The organic extract was dried over anhydrous sodium sulfate and then concentrated. The residue was purified by silica gel chromatography (elution solvent;
dichloromethane:ethanol = 10:1) and formed hydrochloric salt with hydrogen chloride-ether solution. Then, this was recrystallized from ethyl acetate to give 2.60 g of title compound as a colorless powder. Yield: 77 %.

Melting point: 157 - 158.5 °C

Elemental analysis (%): As $C_{20}H_{19}N_3 \cdot HCl \cdot H_2O$

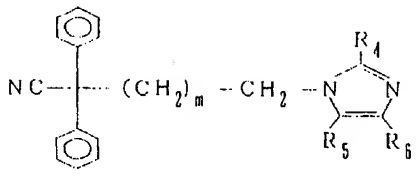
Calculated	C: 67.50	H: 6.23	N: 11.81
Observed	C: 67.55	H: 6.21	N: 11.99

^{1}H-NMR ($CDCl_3$, δ), 7.35 - 7.42 (10H, m), 6.90 (1H, s), 6.77 (1H, s), 3.90 - 3.94 (2H, m), 2.75 - 2.79 (2H, m), 2.25 (3H, s)

(Examples 2 through 10)

[0030] According to the process in Example 1, following compounds were prepared (Table 1).

[Table 1]



Example	R_4	R_5	R_6	m	Salt	Melting point(°C) (Boiling point)	Composition formula	Elemental analysis(%) Calculated/analyzed
2	C_2H_5	H	H	1	HCl	140-141.5	$C_{21}H_{21}N_3 \cdot HCl \cdot 1/5H_2O$	C : 70.95 H : 6.35 N : 11.82 70.80 6.45 11.98
3	i-C_3H_7	H	H	1	—	(230) 0.4mmHg	$C_{22}H_{23}N_3 \cdot 1/5H_2O$	C : 79.34 H : 7.08 N : 12.62 79.47 7.04 11.57
4	H	H	H	1	—	(220) 0.4mmHg	$C_{19}H_{17}N_3 \cdot 1/5H_2O$	C : 78.43 H : 6.03 N : 14.44 78.66 6.20 14.23
5	H	CH_3	CH_3	1	HCl	162-165	$C_{21}H_{21}N_3 \cdot HCl$	C : 71.68 H : 6.30 N : 11.94 71.34 6.35 11.89
6	CH_3	H	H	2	—	123-124	$C_{21}H_{21}N_3$	C : 79.97 H : 6.71 N : 13.32 80.09 6.78 13.15
7	CH_3	H	H	3	HCl	166-167	$C_{23}H_{23}N_3 \cdot HCl \cdot 1/2H_2O$	C : 70.48 H : 6.72 N : 11.21 70.19 6.64 11.09
8	c-C_3H_5	H	H	1	—	(250) 0.7mmHg	$C_{22}H_{21}N_3 \cdot 1/10H_2O$	C : 80.26 H : 6.49 N : 12.76 80.17 6.56 12.67
9	CH_3OCH_2—	H	H	1	—	124-126	$C_{21}H_{21}N_3O$	C : 76.11 H : 6.39 N : 12.68 76.11 6.40 12.29

(Example 10)

4-(2-Methyl-1-imidazolyl)-2,2-diphenylbutylamide

[0031] 4-(2-Methyl-1-imidazolyl)-2,2-diphenylbutyronitrile (7.83 g, 26.0 mmol) and 70 % sulfuric acid (50 ml) were mixed and stirred for 40 minutes at 140 to 150 °C. The solution was made alkaline and extracted with a mixed solvent (5:1) of chloroform with ethanol. The organic extract was dried over anhydrous sodium sulfate and then concentrated. The residue was recrystallized from ethyl acetate-ethanol to give 2.02 g of title compound as colorless needle-like crystals. Yield: 32 %

Melting point: 189 - 190 °C

Elemental analysis (%): As $C_{20}H_{21}N_3O$

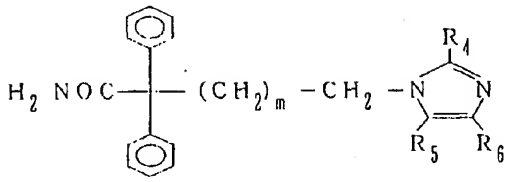
Calculated	C: 75.21	H: 6.63	N: 13.16
Observed	C: 74.98	H: 6.80	N: 13.00

^{1}H-NMR ($CDCl_3$, δ), 7.31 - 7.42 (10H, m), 6.85 (1H, s), 6.73 (1H, s), 5.49 (1H, s), 5.33 (1H, s), 3.77 - 3.82 (2H, m), 2.69 - 2.74 (2H, m), 2.23 (3H, s)

(Examples 11 through 18)

[0032] According to the process in Example 10, following compounds were prepared (Table 2).

[Table 2]



Example	R_4	R_5	R_6	m	Melting point(°C)	Composition formula	Elemental analysis(%) Calculated/analyzed
11	C_2H_5	H	H	1	144-146	$C_{21}H_{23}N_3O$	C : 75.65 H : 6.95 N : 12.60 75.42 7.08 12.43
12	n-C_3H_7	H	H	1	150-152	$C_{22}H_{25}N_3O$	C : 76.05 H : 7.25 N : 12.09 75.98 7.25 12.03
13	i-C_3H_7	H	H	1	176-178	$C_{22}H_{25}N_3O \cdot 1/10H_2O$	C : 75.66 H : 7.27 N : 12.03 75.67 7.30 12.04
14	H	H	H	1	172-175	$C_{19}H_{19}N_3O \cdot 3/5H_2O$	C : 72.17 H : 6.44 N : 13.29 72.20 6.32 12.89
15	H	CH_3	CH_3	1	163-164.5	$C_{21}H_{23}N_3O$	C : 75.65 H : 6.95 N : 12.60 75.37 7.05 12.43
16	H	C_2H_5	C_2H_5	1	194-196	$C_{23}H_{27}N_3O$	C : 76.42 H : 7.53 N : 11.62 76.25 7.64 11.48
17	CH_3	H	H	3	154-156	$C_{22}H_{25}N_3O$	C : 76.05 H : 7.25 N : 12.09 75.96 7.22 11.93
18	t-C_4H_9	H	H	1	136-138	$C_{23}H_{27}N_3O \cdot 1/2H_2O$	C : 74.56 H : 7.62 N : 11.34 74.60 7.46 11.10

(Example 19)

4-(2-Isopropyl-3-methyl-1-imidazolyl)-2,2-diphenylbutylamide·iodide

[0033] A mixture of 4-(2-isopropyl-1-imidazolyl)-2,2-diphenylbutylamide (250 mg, 0.720 mmol), methyl iodide (5.0 ml), acetone (100 ml) and ethanol (1.0 ml) was stirred under heat for 10 hours in a sealed tube. After the solution was concentrated, the residue was recrystallized from ethyl acetate-ethanol to give 0.35 g of title compound as pale yellow needle-like crystals. Yield: 99 %

Melting point: 238 - 239 °C

Elemental analysis (%): As $C_{23}H_{28}IN_3O$

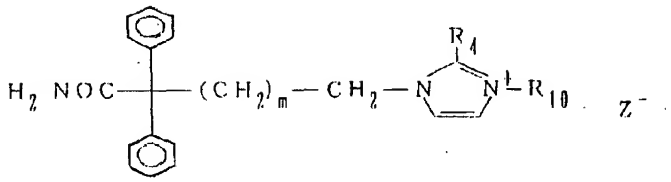
Calculated	C: 56.45	H: 5.77	N: 8.59
Observed	C: 56.35	H: 5.64	N: 8.73

^{1}H-NMR (d_6-DMSO, δ), 7.64 (1H, s), 7.61 (1H, s), 7.46 (1H, s), 7.31 - 7.43 (10H, m), 6.88 (1H, s), 3.81 - 3.88 (5H, m), 3.24 - 3.30 (1H, m), 2.73 - 2.78 (2H, m), 1.16 (6H, d, J = 7.3Hz)

(Examples 20 through 24)

[0034] According to the process in Example 19, following compounds were synthesized (Table 3).

[Table 3]



Example	R_4	R_{10}	m	z	Melting point(°C)	Composition formula	Elemental analysis(%) Calculated/analyzed
20	CH_3	CH_3	1	I	234-236	$C_{21}H_{24}IN_3O \cdot 1/5H_2O$	C : 54.25 H : 5.29 N : 9.04 54.02 5.30 9.00
21	CH_3	C_2H_5	1	I	189-192	$C_{22}H_{26}IN_3O \cdot 3/5H_2O$	C : 54.35 H : 5.64 N : 8.64 54.54 5.78 8.34
22	CH_3	CH_2-	1	Br	230-232	$C_{27}H_{28}BrN_3O$	C : 66.12 H : 5.75 N : 8.57 66.41 5.86 8.68
23	C_2H_5	CH_3	1	I	229-230.5	$C_{22}H_{26}IN_3O$	C : 55.59 H : 5.51 N : 8.84 55.32 5.51 8.94
24	n-C_3H_7	CH_3	1	I	215-216	$C_{23}H_{28}IN_3O$	C : 56.45 H : 5.77 N : 8.59 56.69 5.83 8.89

(Example 25)

3-(2-Methyl-1-imidazolyl)-1,1-diphenylpropanol

[0035] In a 200 ml two-neck flask, under an atmosphere of argon, a solution of ethyl 3-(2-methyl-1-imidazolyl)propionate (3.37 g, 18.5 mmol) in anhydrous tetrahydrofuran was added to 50 ml of 1.8M phenyllithium solution at 0 °C. After stirred for 3.5 hours at 10 °C, the mixture was allowed to stand overnight at room temperature. The solution was poured into water, which was extracted with ethyl acetate. The organic extract was washed with saturated saline solution and dried over anhydrous sodium sulfate, followed by concentration. The residue was purified by silica gel chromatography (elution solvent; ethyl acetate-ethanol = 10:1) and then recrystallized from n-hexaneethyl acetate. This was further recrystallized from ethanolbenzene to give 320 mg of title compound as white needle-like crystals. Yield: 6 %

Melting point: 212 - 214 °C

Elemental analysis (%): As $C_{19}H_{20}N_2O$ $1/10H_2O$

Calculated	C: 77.57	H: 6.92	N: 9.52
Observed	C: 77.66	H: 6.87	N: 9.24

^{1}H-NMR ($CDCl_3$, δ), 7.22 - 7.44 (10H, m), 6.80 (1H, s), 6.72 (1H, 2), 3.79 - 3.84 (2H, m), 2.90 (1H, brs), 2.64 - 2.69 (2H, m), 2.18 (3H, s)

(Example 26)

3-(2-Methyl-1-imidazolyl)-1,1-diphenylbutanol

[0036] Similarly to Example 25, except that 3.60 g (18.3 mmol) of ethyl 3-(2-methyl-1-imidazolyl)butyrate was used in place of ethyl 3-(2-methyl-1-imidazolyl)propionate, 600 mg of title compound were obtained as white cyrstals. Yield: 11 %

Melting point: 168 - 169 °C

Elemental analysis (%): As $C_{20}H_{22}N_2O$ $1/5H_2O$

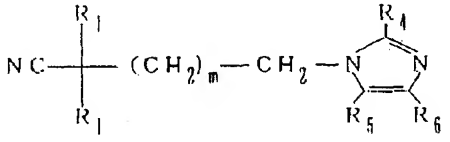
Calculated	C: 77.49	H: 7.28	N: 9.04
Observed	C: 77.21	H: 7.18	N: 8.90

^{1}H-NMR ($CDCl_3$, δ), 7.19 - 7.42 (10H, m), 6.87 (1H, d, J = 2.0Hz), 6.85 (1H, s), 4.25 (1H, sextet, J = 6.2Hz), 2.75 (2H, d, J = 5.9Hz), 2.52 (1H, brs), 2.00 (3H, s), 1.34 (3H, d, J = 6.9Hz)

(Example 27)

[0037] According to the process in Example 1, following compound was synthesized (Table 4).

[Table 4]

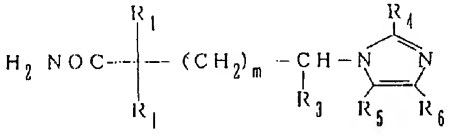


Example	R_1	R_4	R_5	R_6	m	Melting point(°C) (Boiling point)	Composition formula	Elemental analysis(%) Calculated/analyzed
27		CH_3	H	H	1	(240) 0.8mmHg	$C_{20}H_{17}F_2N_3$ · 1/20H_2O	C : 71.01 H : 5.10 N : 12.42 71.39 5.50 12.35

(Examples 28 through 31)

[0038] According to the process in Example 10, following compounds were synthesized (Table 5).

[Table 5]

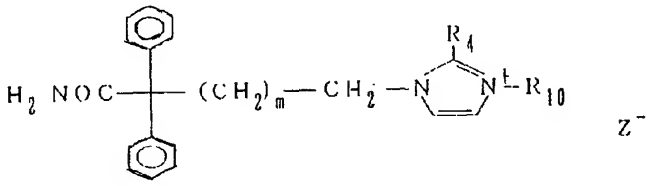


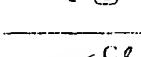
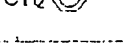
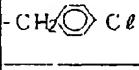
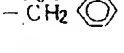
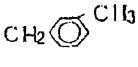
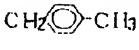
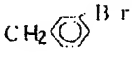
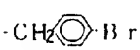
Example	R_1	R_3	R_4	R_5	R_6	m	Melting point(°C)	Composition formula	Elemental analysis Calculated/analyzed
28		H	CH_3	H	H	1	206-207.5	$C_{20}H_{19}F_2N_3O$	C : 67.59 H : 5.39 N : 11.82 67.23 5.55 11.63
29		H	H	n-C_3H_7	n-C_3H_7	1	147-148	$C_{25}H_{31}N_3O$ · 1/5H_2O	C : 76.38 H : 8.05 N : 10.69 76.28 7.79 10.69
30		H	CH_3	H	H	4	159-161	$C_{23}H_{27}N_3O$	C : 76.42 H : 7.53 N : 11.62 76.29 7.53 11.55
31		CH_3	CH_3	H	H	1	148-150	$C_{21}H_{23}N_3O$	C : 75.65 H : 6.95 N : 12.60 75.48 7.16 12.50

(Examples 32 through 51)

[0039] According to the process in Example 19, following compounds were synthesized (Table 6, Table 7).

[Table 6]



Example	R_4	R_{10}	m	z	Melting point(°C)	Composition formula	Elemental analysis Calculated/analyzed
32	CH_3	n-C_3H_7	1	I	173-175	$C_{23}H_{28}IN_3O \cdot 1/5H_2O$	C : 56.04 H : 5.81 N : 8.52 55.89 5.68 8.51
33	CH_3	n-C_4H_9	1	I	164-166	$C_{24}H_{30}IN_3O$	C : 57.26 H : 6.01 N : 8.35 57.08 5.94 8.23
34	CH_3		1	Br	198-199	$C_{27}H_{27}BrClN_3O \cdot 1/5H_2O$	C : 61.36 H : 5.23 N : 7.95 61.16 5.08 7.91
35	CH_3		1	Br	221-222	$C_{27}H_{27}BrClN_3O$	C : 61.78 H : 5.19 N : 8.01 61.54 5.32 7.95
36	CH_3		1	Br	133-135	$C_{27}H_{27}BrClN_3O \cdot 1/2H_2O$	C : 60.74 H : 5.29 N : 7.87 60.78 5.31 7.41
37	CH_3		1	Br	224-226	$C_{28}H_{30}BrN_3O \cdot 3/10H_2O$	C : 65.96 H : 6.05 N : 8.24 66.01 5.96 8.17
38	CH_3		1	Br	210-212	$C_{28}H_{30}BrN_3O \cdot 3/10H_2O$	C : 65.96 H : 6.05 N : 8.24 65.81 5.97 8.02
39	CH_3		1	Br	240-242	$C_{28}H_{30}BrN_3O \cdot 3/10H_2O$	C : 65.96 H : 6.05 N : 8.24 66.00 6.09 8.28
40	CH_3		1	Br	205-206	$C_{27}H_{27}Br_2N_3O$	C : 56.96 H : 4.78 N : 7.38 56.74 4.91 7.60
41	CH_3		1	Br	219-221	$C_{27}H_{27}Br_2N_3O \cdot 3/5i\text{-}PrOH$	C : 57.14 H : 5.29 N : 6.94 56.88 5.50 6.71

[Table 7]

Example	R_4	R_{10}	m	Z	Melting point(°C)	Composition formula	Elemental analysis Calculated/analyzed
42	CH_3	$-CH_2$(2,6-F$_2$-Ph)	1	Br	139-141	$C_{27}H_{26}F_2BrN_3O$ · 1/2EtOH	C : 61.21 H : 5.32 N : 7.65 61.34 5.52 7.38
43	CH_3	$-CH_2$(3,5-F$_2$-Ph)	1	Br	206-208	$C_{27}H_{26}F_2BrN_3O$	C : 61.60 H : 4.98 N : 7.98 61.72 5.14 7.96
44	CH_3	$-CH_2$(2,4-F$_2$-Ph)	1	Br	225-262	$C_{27}H_{26}F_2BrN_3O$	C : 61.60 H : 4.98 N : 7.98 61.38 5.05 7.91
45	CH_3	$-CH_2$(3,4-F$_2$-Ph)	1	Br	215-217	$C_{27}H_{26}F_2BrN_3O$	C : 61.60 H : 4.98 N : 7.98 61.40 5.27 7.79
46	CH_3	$-CH_2$(2,6-Cl$_2$-Ph)	1	Br	273-275	$C_{27}H_{26}BrCl_2N_3O$	C : 57.98 H : 4.69 N : 7.51 57.91 4.75 7.74
47	CH_3	$-CH_2$(4-NO_2-Ph)	1	Br	215-217	$C_{27}H_{27}BrN_4O_3$	C : 60.57 H : 5.08 N : 10.46 60.56 5.19 10.34
48	CH_3	$-CH_2$(Ph)	1	Cl	248-249	$C_{33}H_{32}ClN_3O$	C : 75.92 H : 6.18 N : 8.05 75.54 6.37 7.92
49	CH_3	$-CH_2$(Ph)	3	Br	155-157	$C_{29}H_{32}BrN_3O$ · 1/10H_2O	C : 65.96 H : 6.24 N : 8.08 66.76 6.21 7.97
50	CH_3	$-CH_2$(4-Cl-Ph)	3	Br	205-207	$C_{29}H_{31}BrClN_3O$	C : 62.38 H : 5.70 N : 7.53 62.21 5.90 7.24
51	CH_3	$-CH_2$(Ph)	2	Br	171-173	$C_{28}H_{30}BrN_3O$ · 1/2H_2O	C : 65.50 H : 6.09 N : 8.18 65.37 6.02 8.30

Experimental example

1. Anticholinergic action in guinea-pig ileum and atria

[0040] Male Hartley guinea pigs were sacrificed by blowing on the head and bleeding.

[0041] Ileal segments (about 3 cm long) were suspended in organ baths containing Tyrode solution equilibrated with a mixture of 95 % O_2 and 5 % CO_2 at 32 °C.

[0042] Responses to acetylchloline (ACh) added cumulatively to the baths were isotonically recorded under a tension of 1 g. Dose-response curves of ACh were determined in the absence and presence of test compounds in various concentrations added to the baths 5 min. before ACh application.

[0043] The affinity (pA_2) of test compounds for muscarinic receptor was determined according to Schild method (Arunlakshana, O. and Schild, H.O. (1959) Brit. J. Pharmacol., 14 48-58).

[0044] The isolated atria were suspended under 0.5 g tension in organ baths containing Tyrode solution gassed with 95 % O_2 and 5 % CO_2 at 32 °C.

[0045] Dose-response curves were obtained by cumulative addition of ACh and repeated in the presence of various concentrations of test compounds, allowing 10 min. equilibration time.

[0046] The affinity of test compounds were determined as described for ileum. Results are shown in Table 8.

[Table 8]

No. of examples	Anticholinergic activity (pA_2)	
	Ileum	Atrium
6	8. 95	8. 21
7	8. 17	7. 08
10	10. 16	8. 88
13	9. 17	7. 73
Atropine	8. 67	8. 91
Oxybutynin	8. 44	8. 39

[0047] The compounds of the present invention had a high affinity for muscarinic receptors in guinia pig ileum but a much lower affinity for cardiac receptors.

[0048] In particular, the affinities obtained for compounds of Example 7, 10 and 13 were 10 times greater for receptors in ileum as compared to receptors in heart.

2. Effect on rhythmic bladder contraction

[0049] Male Wistar rats were fixed in supine position under the halothane anesthesia and a balloon-tip catheter was inserted into the bladder through the small incision of apex opening a lower abdomen along the midline, followed by purse-string suture. The catheter was led out of upper end of abdominal incision sutured, connected with a pressure transducer.

[0050] The balloon was filled with about 0.1 to 0.3 ml of water. After the rhythmic contraction of the urinary bladder became constant at a threshold intravesical pressure, test compounds were given intraduodenally. The inhibitory effects were estimated by the reduction in amplitude of bladder contraction. The compounds of the present invention decreased in amplitude of bladder contraction at a dose of 0.03 mg/kg or more.

3. Effect on bethanechol-induced diarrhea

[0051] Test compounds were administered orally to male ICR mice and, 30 min. later 20 mg/kg of bethanechol were given subcutaneously. The appearance of diarrhea was observed from the administration of bethanechol until 0.5 hours later.

[0052] The compounds of the present invention show the inhibitory effects of a dose of 0.06 mg/kg or more.

4. Anticholinergic action in guinea-pig trachea

[0053] Male Hartley guinea-pigs were killed by blowing on the head and bleeding.

[0054] Ring strips of trachea were suspended in organ bath filled with Tyrode solution, kept at 37 °C and gassed with a mixture of 95 % O_2 and 5 % CO_2.

[0055] Responses to ACh were isometrically recorded under a tension of 1 g. Concentration-Response curves were obtained cumulative addition of ACh and repeated in the presence of various concentrations of test compounds, allowing 10 minutes equilibration time.

[0056] The affinity (pA_2) of test compounds for muscarinic receptor was determined according to Schild method (Arunlakshana, O. and Schild, H.O. (1959), Brit. J. Pharmacol., 14 48-58) or van Rossum (van Rossum, J.M. (1963), Arch. Int. Pharmacodyn, Ther., 143 299-330).

Results are shown in Table 9.

[Table 9]

No. of examples	Anticholinergic activity (pA_2)	
	Trachea	Atrium
42	8. 28	7. 54
48	8. 34	7. 52

[Table 9] (continued)

No. of examples	Anticholinergic activity (pA_2)	
	Trachea	Atrium
49	8. 34	7. 70
Ipratropium	8. 85	8. 82

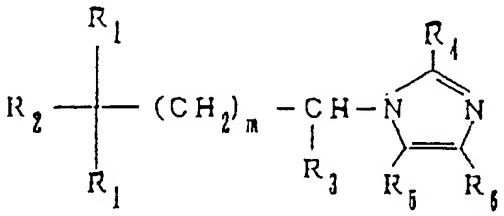
[0057] The affinities (pA_2) of the compounds of the present invention were significantly greater for muscarinic receptors in trachea as compared to receptors in heart.

Utilizability in the industry

[0058] As descried above, the compounds of the present invention will be clinically useful in treating irritable bowel syndrome, dysuria such as pollakiuria and urinary incontinence and chronic respiratory obstructive diseases.

Claims

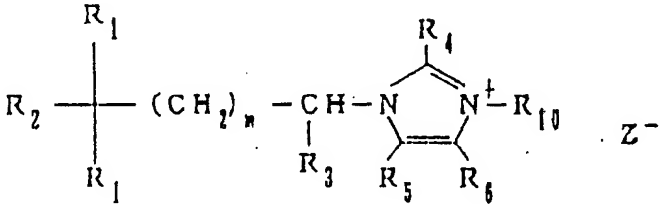
1. Imidazole derivatives represented by a general formula (1)



(1)

[wherein R_1 is a phenyl group which may have halogen substituent or a thienyl group, R_2 is a cyano group, carboxyl group; a $CONR_7R_8$ group (wherein R_7 and R_8 each independently represent hydrogen atom or straight or branched chain alkyl groups having from 1 to 6 carbon atoms, or R_7 and R_8 may form a ring by alkylene chain which may contain oxygen, sulfur or nitrogen hetero atoms) or a $COOR_9$ group (wherein R_9 is a straight or branched chain alkyl group having from 1 to 6 carbon atoms), R_3 is a hydrogen atom or a straight or branched chain alkyl group having from 1 to 6 carbon atoms, R_4, R_5 and R_6 each independently represent hydrogen atom, straight or branched chain alkyl groups having from 1 to 6 carbon atoms which may have substituents selected from the group consisting of halogen, straight or branched chain alkoxy group having from 1 to 6 carbon atoms, hydroxyl group and phenyl group, or cycloalkyl groups having 3 to 8 carbon atoms, and m is an integer from 1 to 6],
and their pharmaceutically acceptable salts.

2. Imdidazole derivatives represented by a general formula (2)



(2)

[wherein R_1, R_2, R_3, R_4, R_5, R_6 and m are defined as in claim 1, R_{10} is a straight or branched chain alkyl group having 1 to 6 carbon atoms or an aralkyl group with straight or branched chain alkylene having 1 to 6 carbom atoms bonded to phenyl group which may have a substituent selected from halogen, straight or branched chain alkyl group having 1 to 6 carbon atoms, straight or branched chain alkoxy groups having 1 to 6 carbon atoms bonded to oxygen atom, nitro group or phenyl group, and Z is a halogen atom],

and their pharmaceutically acceptable salts.

3. Imidazole derivatives of Claim 1, wherein R_1 is a phenyl group and their pharmaceutically acceptable salts.

4. Imidazole derivatives of Claim 1, wherein R_4 is a straight or branched chain alkyl group having from 1 to 6 carbom atoms and their pharmaceutically acceptable salts.

5. Imidazole derivatives of Claim 1, wherein R_2 is a cyano group and their pharmaceutically acceptable salts.

6. Imidazole derivatives of Claim 1, wherein R_2 is an amide group and their pharmaceutically acceptable salts.

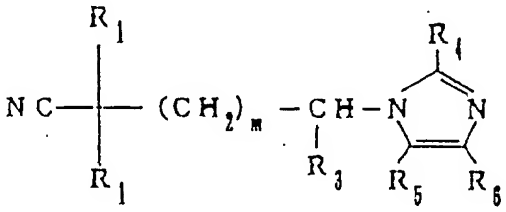
7. Imidazole derivatives of Claim 1, which is 5-(2-methyl-1-imidazolyl)-2,2-diphenylpentanenitrile and their pharmaceutically acceptable salts.

8. Imidazole derivatives of Claim 1, which is 6-(2-methyl-1-imidazolyl)-2,2-diphenylhexanenitrile and their pharmaceutically acceptable salts.

9. Imidazole derivatives of Claim 1, which is 4-(2-methyl-1-imidazolyl)-2,2-diphenylbutylamide and their pharmaceutically acceptable salts.

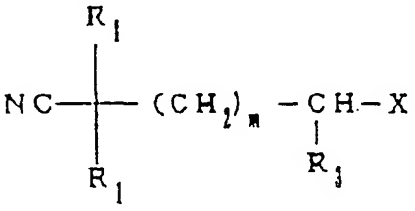
10. Imidazole derivatives of Claim 1, which is 4-(2-isopropyl-1-imidazolyl)-2,2-diphenylbutylamide and their pharmaceutically acceptable salts.

11. A preparative process **characterized in that**, upon preparing compounds represented by a general formula (3)



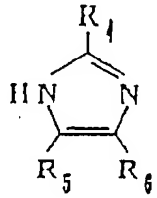
(3)

[wherein R_1, R_3, R_4, R_5, R_6 and m are defined as in claim 1],
and their salts, compounds represented by a general formula (4)



(4)

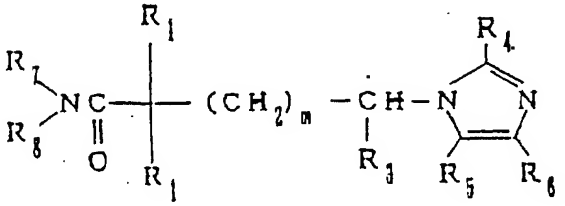
[wherein, R_1, R_3 and m are as defined above, and X denotes a leaving group],
are reacted with compounds represented by a general formula (5)



(5)

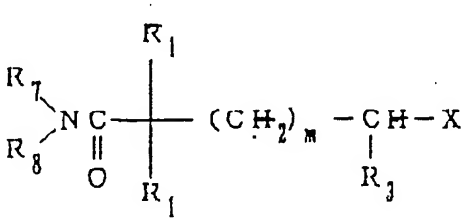
[wherein R_4, R_5 and R_6 are as defined above].

12. A preparative process **characterized in that**, upon preparing compounds represented by a general formula (6)



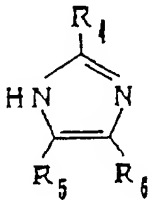
(6)

[wherein R_1, R_3, R_4, R_5, R_6, R_7, R_8 and m are as defined as in claim 1],
and their salts, compounds represented by a general formula (7)



(7)

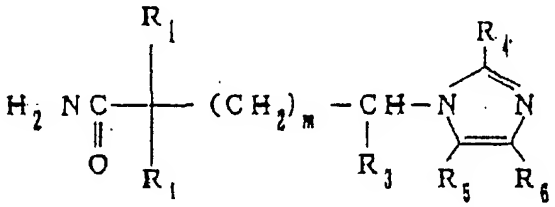
[wherein R_1, R_3, R_7, R_8 and m are as defined above, and X denotes a leaving group],
are reacted with compounds represented by the general formula (5)



(5)

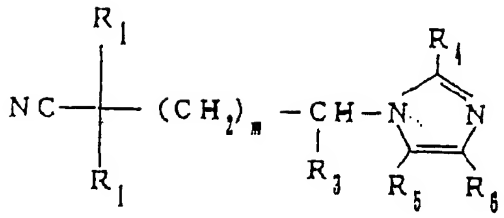
[wherein R_4, R_5 and R_6 are as defined above].

13. A preparative process **characterized in that**, upon preparing compounds represented by a general formula (8)



(8)

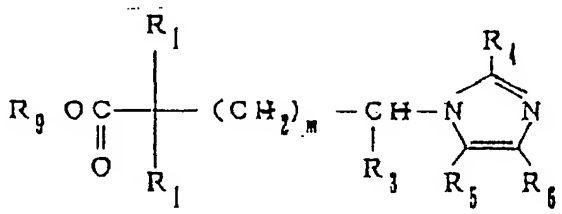
[wherein R_1, R_3, R_4, R_5, R_6 and m are as defined as in claim 1],
and their salts, compounds represented by a general formula (3)



(3)

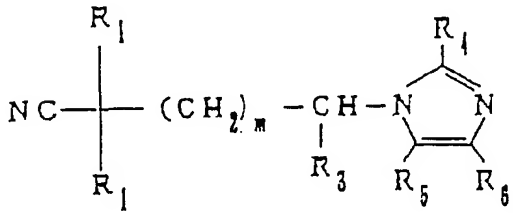
[wherein R_1, R_3, R_4, R_5, R_6 and m are same as above],
are hydrolyzed.

14. A preparative process **characterized in that**, upon preparing compounds represented by a general formula (9)



(9)

[wherein R_1, R_3, R_4, R_5, R_6, R_9 and m are as defined as in claim 1], compounds represented by a general formula (3)



(3)

[wherein R_1, R_3, R_4, R_5, R_6 and m are same as above].
are alcoholyzed.

15. A preparative process **characterized in that**, upon preparing compounds represented by the general formula (2) as defined in claim 2, compounds represented by the general formula (1) as defined in claim 1 are reacted with compounds represented by a general formula (13)

$$R_{10} - Z \qquad (13)$$

[wherein R_{10} and Z are as defined in claim 2].

16. Imidazole derivatives as defined in claim 1 for use as a medicament.

17. Imidazole derivatives as defined in claim 2 for use as a medicament.

18. A pharmaceutical composition, containing imidazole derivatives as defined in claim 1 or 2, their pharmaceutically acceptable salts and pharmaceutically acceptable excipients for use as antagonists against cholinergic receptor.

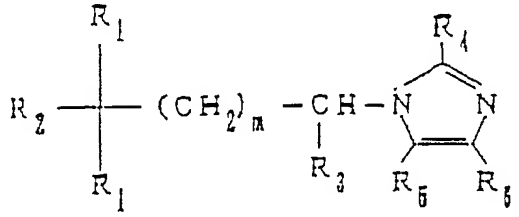
19. A pharmaceutical composition, containing imidazole derivatives as defined in claim 1 or 2, their pharmaceutically acceptable salts and pharmaceutically acceptable excipients for use in treatment of urinary disorder.

20. A pharmaceutical composition, containing imidazole derivatives as defined in claim 1 or 2, their pharmaceutically acceptable salts and pharmaceutically acceptable excipients for use in treatment of irritable bowel syndrome.

21. A pharmaceutical composition, containing imidazole derivatives as defined in claim 1 or 2, their pharmaceutically acceptable salts and pharmaceutically acceptable excipients for use in treatment of chronic respiratory obstructive diseases.

Patentansprüche

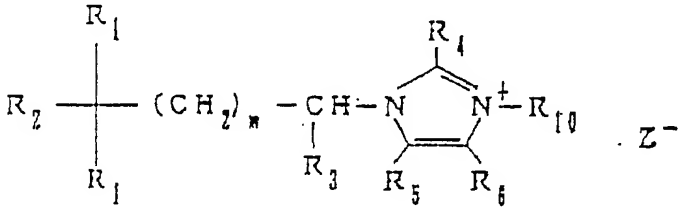
1. Imidazolderivate der allgemeinen Formel (1)



(1)

[worin R_1 eine Phenylgruppe, welche einen Halogensubstituenten aufweisen kann, oder eine Thienylgruppe ist, R_2 eine Cyanogruppe, Carboxylgruppe; eine $CONR_7R_8$-Gruppe (worin R_7 und R_8 jeweils unabhängig Wasserstoffatom oder gerad- oder verzweigtkettige Alkylgruppen mit 1 bis 6 Kohlenstoffatomen bedeuten, oder R_7 und R_8 einen Ring bilden können durch eine Alkylenkette, welche Sauerstoff, Schwefel oder Stickstoff-Heteroatome enthalten kann) oder eine $COOR_9$-Gruppe (worin R_9 eine gerad- oder verzweigtkettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen bedeutet) ist, R_3 ein Wasserstoffatom oder eine gerad- oder verzweigtkettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist; R_4, R_5 und R_6 jeweils unabhängig ein Wasserstoffatom, gerad- oder verzweigtkettige Alkylgruppen mit 1 bis 6 Kohlenstoffatomen, welche Substituenten aufweisen können, gewählt aus der Gruppe, bestehend aus Halogen, gerad- oder verzweigtkettige Alkoxygruppe mit 1 bis 6 Kohlenstoffatomen, Hydroxylgruppe und Phenylgruppe, oder Cycloalkylgruppen mit 3 bis 8 Kohlenstoffatomen bedeuten, und m eine ganze Zahl von 1 bis 6 ist],
und deren pharmazeutisch annehmbaren Salze.

2. Imidazolderivate der allgemeinen Formel (2)



(2)

[worin R_1, R_2, R_3, R_4, R_5, R_6 und m wie in Anspruch 1 definiert sind, R_{10} eine gerad- oder verzweigtkettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen oder eine Aralkylgruppe mit gerad- oder verzweigtkettigem Alkylen mit 1 bis 6 Kohlenstoffatomen, gebunden an Phenylgruppe, welche einen Substituenten aufweisen kann, gewählt aus Halogen, gerad- oder verzweigtkettiger Alkylgruppe mit 1 bis 6 Kohlenstoffatomen, gerad- oder verzweigtkettigen Alkoxygruppen mit 1 bis 6 Kohlenstoffatomen, gebunden an Sauerstoffatom, Nitrogruppe oder Phenylgruppe, ist, und Z ein Halogenatom ist],
und deren pharmazeutisch annehmbaren Salze.

3. Imidazolderivate nach Anspruch 1, wobei R_1 eine Phenylgruppe ist, und deren pharmazeutisch annehmbaren Salze.

4. Imidazolderivate nach Anspruch 1, wobei R_4 eine gerad- oder verzweigtkettige Alkylgruppe mit 1 bis 6 Kohlenstoffatomen ist, und deren pharmazeutisch annehmbaren Salze.

5. Imidazolderivate nach Anspruch 1, wobei R_2 eine Cyanogruppe ist, und deren pharmazeutisch annehmbaren Salze.

6. Imidazolderivate nach Anspruch 1, wobei R_2 eine Amidgruppe ist, und deren pharmazeutisch annehmbaren Salze.

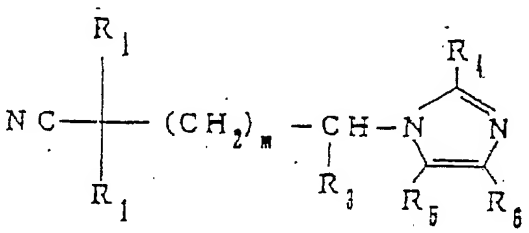
7. Imidazolderivate nach Anspruch 1, nämlich 5-(2-Methyl-1-imidazolyl)-2,2-diphenylpentannitril und deren pharmazeutisch annehmbaren Salze.

8. Imidazolderivate nach Anspruch 1, nämlich 6-(2-Methyl-1-imidazolyl)-2,2-diphenylhexannitril und deren pharmazeutisch annehmbaren Salze.

9. Imidazolderivate nach Anspruch 1, nämlich 4-(2-Methyl-1-imidazolyl)-2,2-diphenylbutylamid und deren pharmazeutisch annehmbaren Salze.

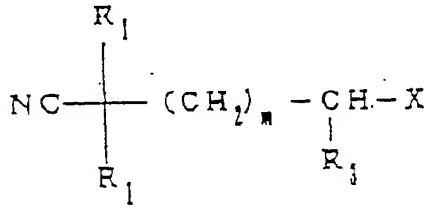
10. Imidazolderivate nach Anspruch 1, nämlich 4-(2-Isopropyl-1-imidazolyl)-2,2-diphenylbutylamid und deren pharmazeutisch annehmbaren Salze.

11. Herstellungsverfahren, **dadurch gekennzeichnet, daß** bei der Herstellung von Verbindungen der allgemeinen Formel (3)



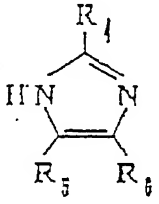
(3)

[worin R_1, R_3, R_4, R_5, R_6 und m wie in Anspruch 1 definiert sind],
und deren Salzen, Verbindungen der allgemeinen Formel (4)



(4)

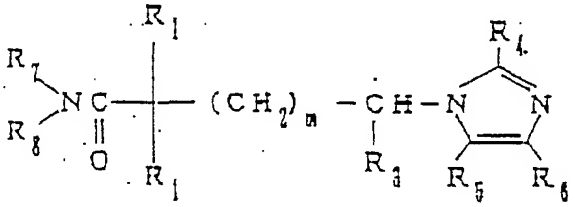
[worin R_1, R_3 und m wie oben definiert sind, und X eine Abgangsgruppe bezeichnet],
mit Verbindungen der allgemeinen Formel (5) umgesetzt werden



(5)

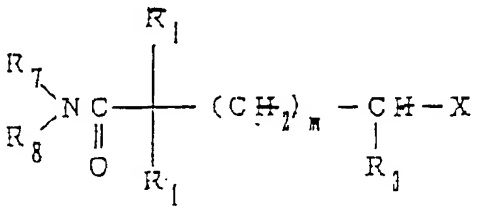
[worin R_4, R_5 und R_6 wie oben definiert sind].

12. Herstellungsverfahren, **dadurch gekennzeichnet, daß** bei der Herstellung von Verbindungen der allgemeinen Formel (6)



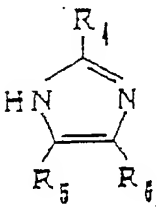
(6)

[worin R_1, R_3, R_4, R_5, R_6, R_7, R_8 und m wie in Anspruch 1 definiert sind],
und deren Salzen, Verbindungen der allgemeinen Formel (7)



(7)

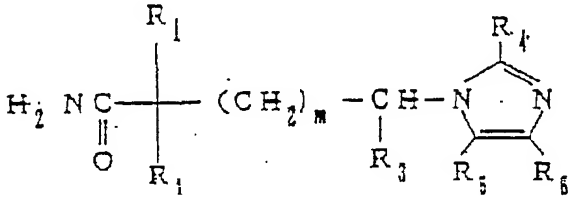
[worin R_1, R_3, R_7, R_8 und m wie oben definiert sind, und X eine Abgangsgruppe bedeutet],
umgesetzt werden mit Verbindungen der allgemeinen Formel (5)



(5)

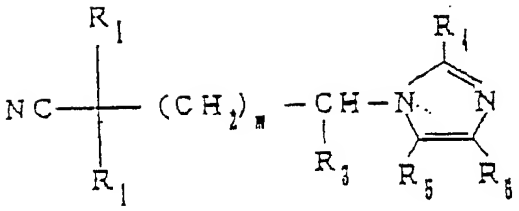
[worin R_4, R_5 und R_6 wie oben definiert sind].

13. Herstellungsverfahren, **dadurch gekennzeichnet, daß** bei der Herstellung von Verbindungen der allgemeinen Formel (8)



(8)

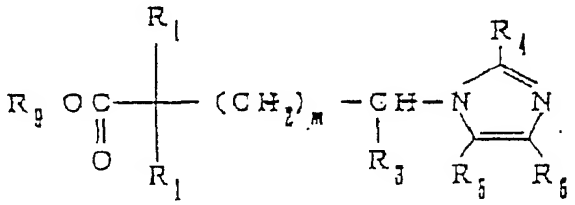
[worin R_1, R_3, R_4, R_5, R_6 und m wie in Anspruch 1 definiert sind],
und deren Salzen, Verbindungen der allgemeinen Formel (3)



(3)

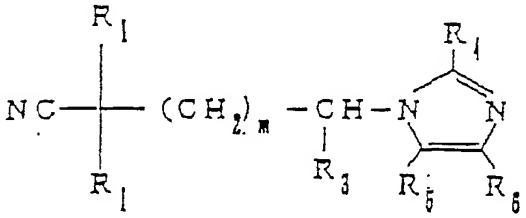
[worin R_1, R_3, R_4, R_5, R_6 und m wie oben definiert sind],
hydrolysiert werden..

14. Herstellungsverfahren, **dadurch gekennzeichnet, daß** bei der Herstellung von Verbindungen der allgemeinen Formel (9)



(9)

[worin R_1, R_3, R_4, R_5, R_6, R_9 und m wie in Anspruch 1 definiert sind],
Verbindungen der allgemeinen Formel (3)



(3)

[worin R_1, R_3, R_4, R_5, R_6 und m wie oben definiert sind],
alkoholisiert werden.

15. Herstellungsverfahren, **dadurch gekennzeichnet, daß** bei der Herstellung von Verbindungen der allgemeinen Formel (2) wie in Anspruch 2 definiert, Verbindungen der allgemeinen Formel (1), wie in Anspruch 1 definiert, umgesetzt werden mit Verbindungen der allgemeinen Formel (13)

$$R_{10} - Z \qquad (13)$$

[worin R_{10} und Z wie in Anspruch 2 definiert sind].

16. Imidazolderivate nach Anspruch 1 zur Verwendung als Arzneimittel.

17. Imidazolderivate nach Anspruch 2 zur Verwendung als Arzneimittel.

18. Pharmazeutische Zusammensetzung, enthaltend Imidazolderivate wie in Anspruch 1 oder 2 definiert, deren pharmazeutisch annehmbaren Salze und pharmazeutisch annehmbare Träger, zur Verwendung als Antagonisten ge-

genüber cholinergischem Rezeptor.

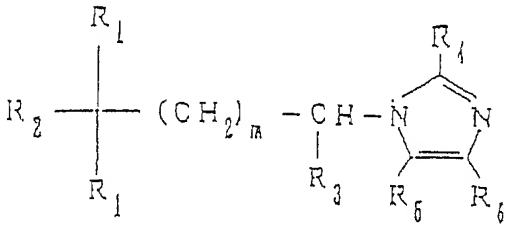
19. Pharmazeutische Zusammensetzung, enthaltend Imidazolderivate wie in Anspruch 1 oder 2 definiert, deren pharmazeutisch annehmbaren Salze und pharmazeutisch annehmbare Träger, zur Verwendung bei der Behandlung einer Harnstörung.

20. Pharmazeutische Zusammensetzung, enthaltend Imidazolderivate wie in Anspruch 1 oder 2 definiert, deren pharmazeutisch annehmbaren Salze und pharmazeutisch annehmbare Träger, zur Verwendung bei der Behandlung des Reizdarmsyndroms.

21. Pharmazeutische Zusammensetzung, enthaltend Imidazolderivate wie in Anspruch 1 oder 2 definiert, deren pharmazeutisch annehmbaren Salze und pharmazeutisch annehmbare Träger, zur Verwendung bei der Behandlung chronischer obturierender Atmungskrankheiten.

Revendications

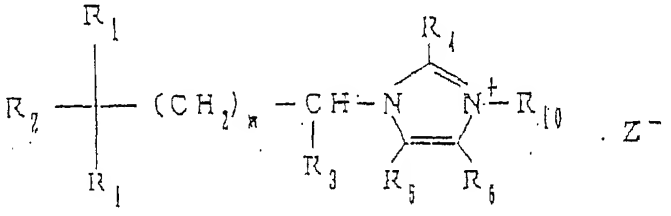
1. Dérivés d'imidazole représentés par la formule générale (1) :



(1)

[dans laquelle R_1 représente un groupe phényle qui peut comporter un substituant halogéné ou un groupe thiényle, R_2 représente un groupe cyano ou un groupe carboxyle ; un groupe $CONR_7\ R_8$ (dans lequel R_7 et R_8 représentent indépendamment chacun un atome d'hydrogène ou des groupes alkyle à chaîne linéaire ou ramifiée comportant de 1 à 6 atomes de carbone, ou R_7 et R_8 peuvent former un cycle par une chaîne alkylène qui peut contenir des hétéroatomes d'oxygène, de soufre ou d'azote) ou un groupe $COOR_9$ (dans lequel R_9 représente un groupe alkyle à chaîne linéaire ou ramifiée comportant de 1 à 6 atomes de carbone), R_3 représente un atome d'hydrogène ou un groupe alkyle à chaîne linéaire ou ramifiée comportant de 1 à 6 atomes de carbone, R_4, R_5 et R_6 représentent indépendamment chacun un atome d'hydrogène, des groupes alkyle à chaîne linéaire ou ramifiée comportant de 1 à 6 atomes de carbone qui peuvent comporter des substituants choisis parmi un atome d'halogène, un groupe alkoxy à chaîne linéaire ou ramifiée comportant de 1 à 6 atomes de carbone, un groupe hydroxy et un groupe phényle, des groupes cycloalkyle comportant de 3 à 8 atomes de carbone, et m est un entier de 1 à 6], et leurs sels pharmaceutiquement acceptables.

2. Dérivés d'imidazole représentés par la formule générale (2) :



(2)

[dans laquelle R_1, R_2, R_3, R_4, R_5, R_6 et m sont définis dans la revendication 1, R_{10} représente un groupe alkyle à chaîne linéaire ou ramifiée comportant de 1 à 6 atomes de carbone ou un groupe aralkyle comportant un groupe alkylène à chaîne linéaire ou ramifiée comportant de 1 à 6 atomes de carbone lié à un groupe phényle qui peut

comporter un substituant choisi parmi un atome d'halogène, un groupe alkyle à chaîne linéaire ou ramifiée comportant de 1 à 6 atomes de carbone, les groupes alkoxy à chaîne linéaire ou ramifiée comportant de 1 à 6 atomes de carbone liés à un atome d'oxygène, un groupe nitro ou un groupe phényle, et Z représente un atome d'halogène], et leurs sels pharmaceutiquement acceptables.

3. Dérivés d'imidazole selon la revendication 1, dans lesquels R_1 représente un groupe phényle, et leurs sels pharmaceutiquement acceptables.

4. Dérivés d'imidazole selon la revendication 1, dans lesquels R_4 représente un groupe alkyle à chaîne linéaire ou ramifiée comportant de 1 à 6 atomes de carbone et leurs sels pharmaceutiquement acceptables.

5. Dérivés d'imidazole selon la revendication 1, dans lesquels R_2 représente un groupe cyano et leurs sels pharmaceutiquement acceptables.

6. Dérivés d'imidazole selon la revendication 1, dans lesquels R_2 représente un groupe amide et leurs sels pharmaceutiquement acceptables.

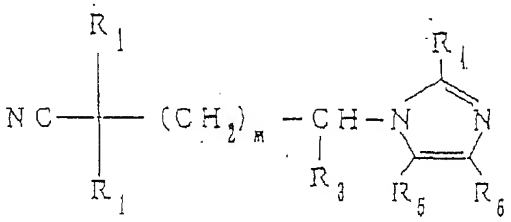
7. Dérivé d'imidazole selon la revendication 1, qui est le 5-(2-méthyl-1-imidazolyl)-2,2-diphénylpentanenitrile et ses sels pharmaceutiquement acceptables.

8. Dérivé d'imidazole selon la revendication 1, qui est le 6-(2-méthyl-1-imidazolyl)-2,2-diphénylhexanenitrile et ses sels pharmaceutiquement acceptables.

9. Dérivé d'imidazole selon la revendication 1, qui est le 4-(2-méthyl-1-imidazolyl)-2,2-diphénylbutylamide et ses sels pharmaceutiquement acceptables.

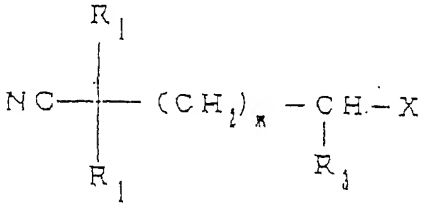
10. Dérivé d'imidazole selon la revendication 1, qui est le 4-(2-isopropyl-1-imidazolyl)-2,2-diphénylbutylamide et ses sels pharmaceutiquement acceptables.

11. Procédé de préparation **caractérisé en ce que** pour préparer les composés représentés par la formule générale (3) :



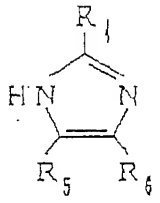
(3)

[dans laquelle R_1, R_3, R_4, R_5, R_6 et m sont tels que définis dans la revendication 1], et leurs sels, on fait réagir des composés représentés par la formule générale (4) :



(4)

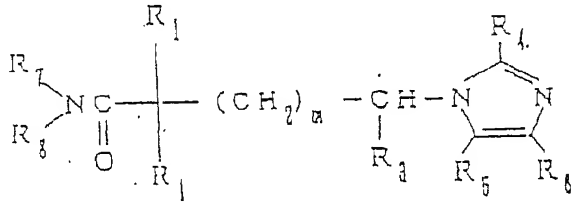
[dans laquelle R_1, R_3 et m sont tels que définis ci-dessus, et X représente un groupe partant], avec des composés représentés par la formule générale (5) :



(5)

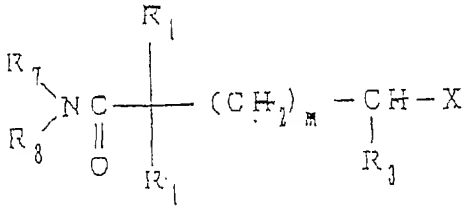
[dans laquelle R_4, R_5 et R_6 sont tels que définis ci-dessus].

12. Procédé de préparation **caractérisé en ce que** pour préparer les composés représentés par la formule générale (6) :



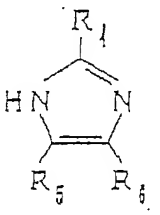
(6)

[dans laquelle R_1, R_3, R_4, R_5, R_6, R_7 et m sont tels que définis dans la revendication 1], et leurs sels, on fait réagir des composés représentés par la formule générale (7) :



(7)

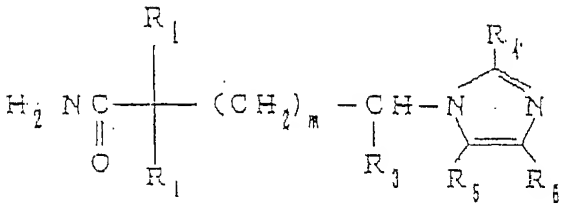
[dans laquelle R_1, R_3, R_7, R_8 et m sont tels que définis ci-dessus, et X représente un groupe partant], avec des composés représentés par la formule générale (5) :



(5)

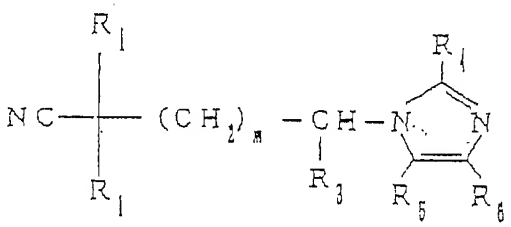
[dans laquelle R_4, R_5 et R_6 sont tels que définis ci-dessus] .

13. Procédé de préparation **caractérisé en ce que** pour préparer les composés représentés par la formule générale (8) :



(8)

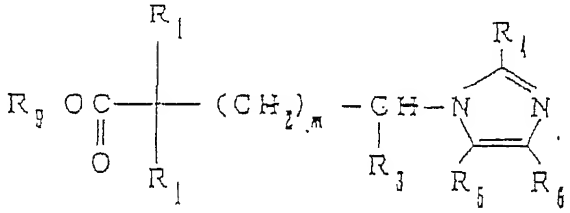
[dans laquelle R_1, R_3, R_4, R_5, R_6 et m sont tels que définis dans la revendication 1] , et leurs sels, on hydrolyse des composés représentés par la formule générale (3) :



(3)

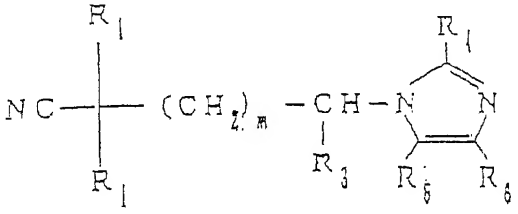
[dans laquelle R_1, R_3, R_4, R_5, R_6 et m sont les mêmes que ci-dessus]

14. Procédé de préparation **caractérisé en ce que** pour préparer les composés représentés par la formule générale (9) :



(9)

[dans laquelle R_1, R_3, R_4, R_5, R_6, R_9 et m sont tels que définis dans la revendication 1], on convertit en alcool des composés représentés par la formule générale (3) :



(3)

[dans laquelle R_1, R_3, R_4, R_5, R_6 et m sont les mêmes que ci-dessus].

15. Procédé de préparation **caractérisé en ce que** pour préparer les composés représentés par la formule générale (2) telle que définie dans la revendication 2, on fait réagir des composés représentés par la formule générale (1) telle que définie dans la revendication 1 avec des composés représentés par la formule générale (13) :

$$R_{10} - Z \quad (13)$$

[dans laquelle R_{10} est Z sont tels que définis dans la revendication 2].

16. Dérivés d'imidazole tels que définis dans la revendication 1 destinés à être employés comme médicament.

17. Dérivés d'imidazole tels que définis dans la revendication 2, destinés à être employés comme médicament.

18. Composition pharmaceutique contenant des dérivés d'imidazole tels que définis dans la revendication 1 ou 2, leurs sels pharmaceutiquement acceptables et des excipients pharmaceutiquement acceptables, pour une utilisation comme antagonistes du récepteur cholinergique.

19. Composition pharmaceutique contenant des dérivés d'imidazole selon la revendication 1 ou 2, leurs sels pharmaceutiquement acceptables et des excipients pharmaceutiquement acceptables, pour une utilisation dans le traitement d'un trouble urinaire.

20. Composition pharmaceutique contenant des dérivés d'imidazole selon la revendication 1 ou 2, leurs sels pharmaceutiquement acceptables et des excipients pharmaceutiquement acceptables, pour une utilisation dans le traitement du syndrome de l'intestin irritable.

21. Composition pharmaceutique contenant des dérivés d'imidazole tels que définis dans la revendication 1 ou 2, leurs sels pharmaceutiquement acceptables et des excipients pharmaceutiquement acceptables, pour une utilisation dans le traitement des affections respiratoires obstructives chroniques.